New Catalytic Reactions of Oxa- and Azabicyclic Alkenes

DINESH KUMAR RAYABARAPU‡ AND CHIEN-HONG CHENG*

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan

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ABSTRACT

Bicyclic alkenes, including oxa- and azabenzonorbornadienes and their derivatives, can be readily activated by transition metal complexes face-selectively due to their unsymmetrical bicyclic structure and the intrinsic angle strain on the carbon–carbon double bond. We have developed several stereo-, regio-, and chemoselective reactions catalyzed by nickel and palladium complexes using these bicyclic alkenes as substrates, providing a unique means of constructing a variety of synthetically useful carbocycles and heterocycles with high efficiency not generally accessible by traditional methods. This Account outlines these new metal-catalyzed reactions that include couplings, cycloadditions, and cyclization reactions.

Introduction

Transition metal catalysts provide an excellent tool for generating complex organic molecules in a single step from readily available starting substrates in a stereo-, regio-, and chemoselective fashion, which is generally not possible using traditional organic synthesis.[1] However, the development of new metal-catalyzed reactions with excellent regio- and stereoselectivity remains an exciting challenge to organic chemists. Bicyclic alkenes, including oxa- and azabenzonorbornadienes and their derivatives, a class of 1,4-epoxides, can be readily activated by transition metal complexes face-selectively due to their unsymmetrical bicyclic structure and the intrinsic angle strain on the carbon–carbon double bond. Intrigued by the unexploited synthetic potential of this class of synthons, we have embarked on a research program on "chemistry of oxa- and azabicyclic olefins" with the main aim of evolving new synthetic methodologies using nickel, palladium, and cobalt complexes as catalysts in the past decade. Recently, Lautens' group wrote an excellent review on the enantioselective ring opening of oxabicyclic alkenes.[2] In this Account, we summarize various new reactions of oxa- and azabicyclic olefins, which involve cycloaddition, cyclization, and coupling strategies. Figure 1 outlines the three different kinds of oxa- or azabicyclic systems used in these reactions.

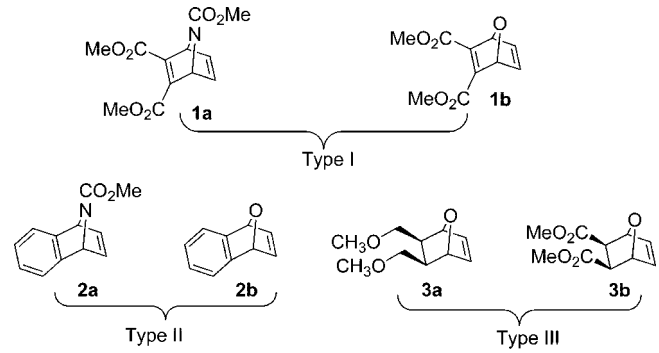

FIGURE 1. Bicyclic olefins used in the catalytic reactions.

In 1971, Caple and co-workers showed the first example of ring opening of oxabicyclic systems using alkyl nucleophiles such as BuLi to afford ring opening products.[3] In 1989, Lautens and co-workers demonstrated the alkylative ring opening of oxabicycles with organocuprate reagents.[4] Later, Plumet also showed the ring opening of oxabicycles using alkyllithium reagents.[5] Lautens' group also demonstrated the first example of an asymmetric ring opening of a [3.2.1]oxabicycle using BuLi in the of presence of sparteine.[6] In 1995, Moinet and Fiaud reported a palladium-catalyzed enantioselective ring opening of oxabicyclic alkenes using phenyl triflate.[7] In 1993, we reported the reductive coupling of organic halides with oxa- and azabicyclic alkenes, thus initiating our research of oxa- and azabicyclic alkene chemistry.[8]

Coupling Reactions of Oxabicyclic Alkenes

Bicyclic alkene **1a** or **1b** reacted with iodobenzene in the presence of $PdCl_2(PPh_3)_2$ and zinc powder in toluene at 80 °C to give **4a** in 60% yield (Scheme 1).[8] The reaction also works with other aromatic iodides, affording various biaryl compounds. This route offers a unique and convenient path for the synthesis of biaryl compounds and even heteroaromatics in moderate to good yields.

A possible mechanism is shown in Scheme 2 involving the initial reduction of Pd(II) to Pd(0) by zinc metal, oxidative addition of R1I to Pd(0) species to yield

Dinesh Kumar Rayabarapu was born in Hyderabad (AP), India. He received his bachelor's degree from Osmania University in 1995 and his master's degree from the University of Hyderabad (1997). He obtained his Ph.D. in 2002 from National Tsing Hua University working with Prof. Chien-Hong Cheng on transition metal-catalyzed organic synthesis. Subsequently, he pursued his postdoctoral work in the same laboratory for two years in the area of ring opening reactions and synthesis of organic light-emitting materials. Then he moved to the University of Kansas, to work with Prof. Jon Tunge in the area of synthesis via decarboxylative coupling chemistry. Currently, he is a research associate with Prof. Paul R. Hanson working on the design and synthesis of *S*- and *P*-heterocycles for high-throughput chemistry. His research interests include transition metal-catalyzed organic synthesis, asymmetric catalysis, and the development of combinatorial libraries.

Chien-Hong Cheng received his B.S. degree in chemistry from National Tsing Hua University (NTHU) in 1971. He earned his Ph.D. from the University of Rochester with Prof. Richard Eisenberg in 1978 and pursued postdoctoral work in the same laboratory (1978–1979). In 1979, he returned to the Department of Chemistry of NTHU as an Associate Professor (1979–1984), where he is currently a Professor. He was a visiting scientist at the Department of Chemistry of Princeton University (1984–1985). He served as the Chairman of the Department of Chemistry of NTHU from 1990–1993 and currently serves as the Director General of the Department of Natural Sciences, National Science Council, Taiwan. He was the recipient of the Outstanding Research Award of the National Science Council (1988–1990, 1991–1995) and the Ministry of Education Science Award in 2002. He has been a Chair Professor at NTHU since 2003 and was a National Chair Professor, Ministry of Education, from 2004 to 2006. His research interests include the development of new synthetic methods using organometallic compounds as catalysts and organic materials in optoelectronics.

* E-mail: chcheng@mx.nthu.edu.

‡ Current address: Department of Chemistry, 2010 Malott Hall, University of Kansas, Lawrence, KS 66045.

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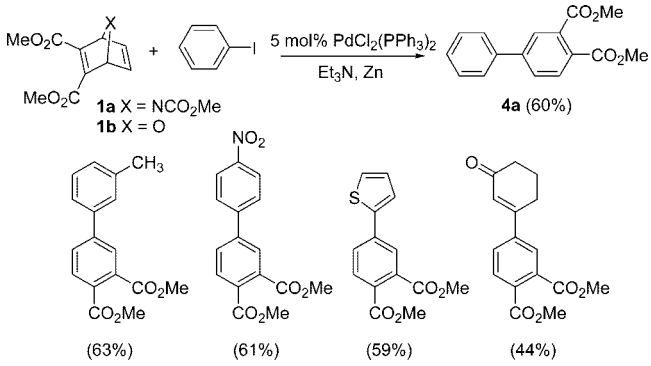
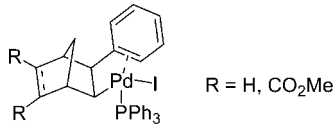
Scheme 1



R1PdI(PPh_3)$_2$ (**5**), and exo addition of R1-Pd to substrate **1** to yield **6**, followed by β-heteroatom elimination to give intermediate **7**. Protonation of the last species affords *cis*-dihydro product **8** and a Pd(II) species. Further deamination or dehydration of the organic compound **8** affords aryl product **4**, while reduction of the Pd(II) species by Zn metal to Pd(0) completes the catalytic cycle.

An alternative mechanism which cannot be totally ruled out would be reduction of the C–Pd bond by Zn in intermediate **6** to form Pd(0) and the bicyclozinc species (similar to intermediate **6** with Zn in place of Pd) which undergoes β-oxygen elimination leading to intermediate **7**.

In agreement with the proposed mechanism, the reaction of **1a** with a stoichiometric amount of PhPdI(PPh_3)$_2$ yielded the biaryl product **4a**. Although attempts to isolate or to detect **6** failed, the proposed structure of **6** and exo addition of PhPdI(PPh_3)$_2$ to **1a** gained strong support from the observation that reaction of PhPdI(PPh_3)$_2$ with norbornadiene or norbornene yielded the Pd complex **9**, in which the aryl group and the Pd center are all at exo positions.[9]



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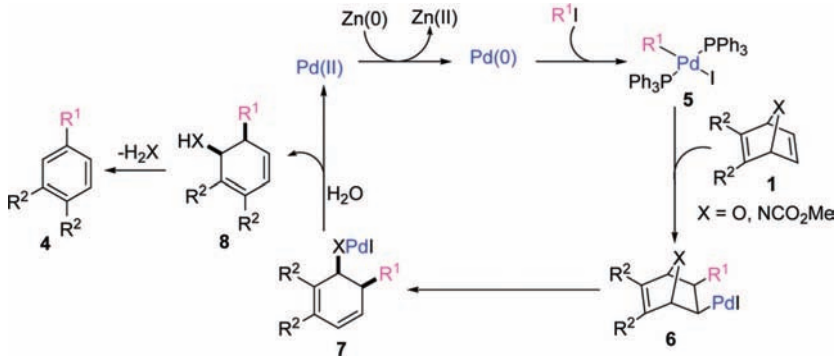
When the catalytic reaction was extended to 7-azabenzonorbornadiene **2a** in the presence of the $PdCl_2(PPh_3)_2$–Zn–Et_3N catalyst system, a mixture of 2-phenylnaphthalene and methyl *N*-(*cis*-1,2-dihydro-l-naphthyl)carbamate **10a** in 15 and 66% yields, respectively, was obtained (Scheme 3).[3b] Similarly, 2-phenyl naphthalene and **10b** were produced when 7-oxabenzonorbornadiene **2b** was used. The addition of $ZnCl_2$ and Et_3N to the catalytic system greatly improves the yield of **10**. A variety of aromatic iodides, β-iodoenone, and benzyl bromide also reacted with **2** to give **10** as the syn diastereomers exclusively in excellent yields. The dihydronaphthalene skeleton is found in a range of naturally occurring compounds that exhibit diverse biological activities.[10–12]

Another complementary route to the *cis*-1,2-dihydro-1-naphthol and *N*-(*cis*-1,2-dihydro-l-naphthyl)carbamate derivatives was realized by the utilization of nickel catalysis.[13] Nickel complexes catalyze the ring opening addition of various organic halides to not only 7-heteroatom benzonorbornadiene but also highly substituted 7-oxanorbornenes to yield products with multiple stereocenters (Scheme 4). For example, the addition of iodobenzene to compound **3a** in acetonitrile in the presence of $Ni(PPh_3)_2Cl_2$ and zinc occurs at 70 °C, affording completely stereoselective ring opening product **11a**. Benzyl bromide and β- and α-bromostyrenes also give ring opening addition products **11b–d** in good yields. The styryl group in compound **11c** was found to be *trans*, although a mixture of both *cis*- and *trans*-β-bromostyrene was used at the beginning of the addition reaction. Highly substituted cyclohexenol **11e** was obtained in stereoselective fashion via electrophilic ring opening.

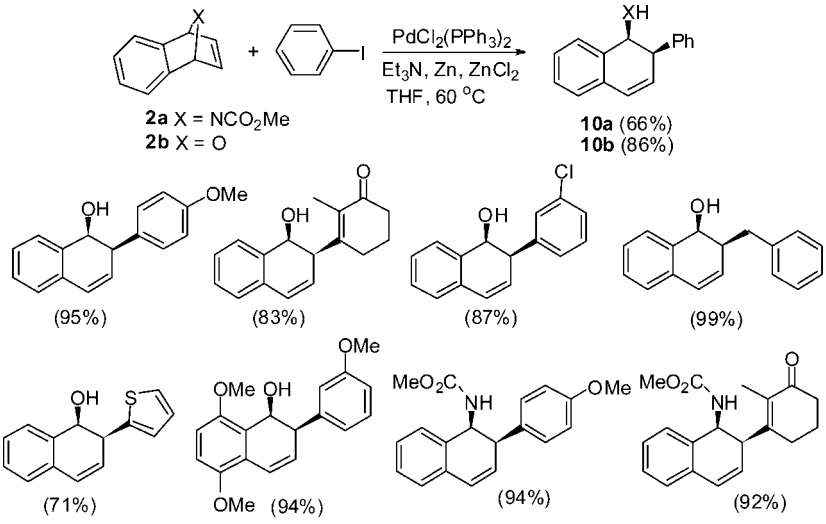
In general, the palladium-catalyzed ring opening reactions were carried out in THF at 60 °C in the presence of Zn, $ZnCl_2$, and Et_3N, whereas the nickel-catalyzed reactions were performed in acetonitrile in the presence of Zn at 70 °C. The time required for the completion of reaction is ca. 2–3 times shorter for the nickel system than for the palladium system. The palladium system does not effectively catalyze the ring opening of norbornene derivatives **3** with aryl iodides. Very recently, Martin's group reported a modified condition using $Pd(OAc)_2$, PPh_3, Zn, and 1,2,2,6,6-pentamethylpiperidine in DMF for the synthesis of 1,2-dihydro-1-naphthols.[14]

Our efforts in the ring opening of oxabicyclic alkenes by hydrosilylation led to the discovery of a novel method for the synthesis of various substituted biaryls. It is known that the addition of a H–Si bond to an unsaturated

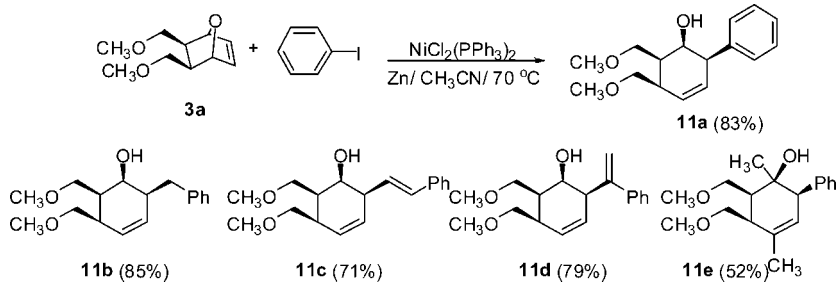
Scheme 2



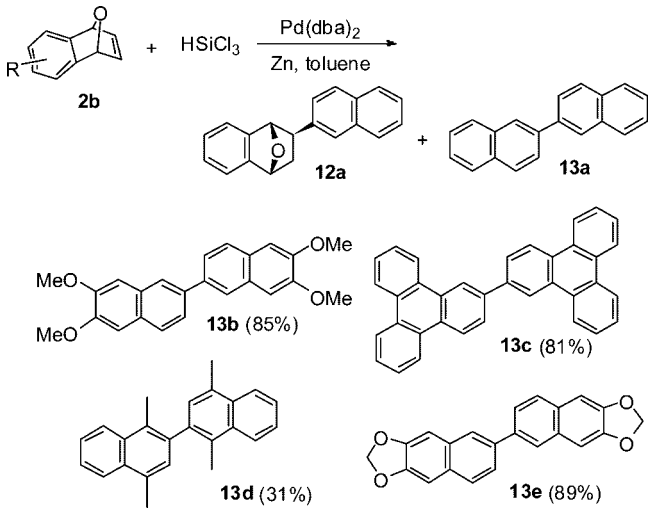
Scheme 3



Scheme 4



Scheme 5

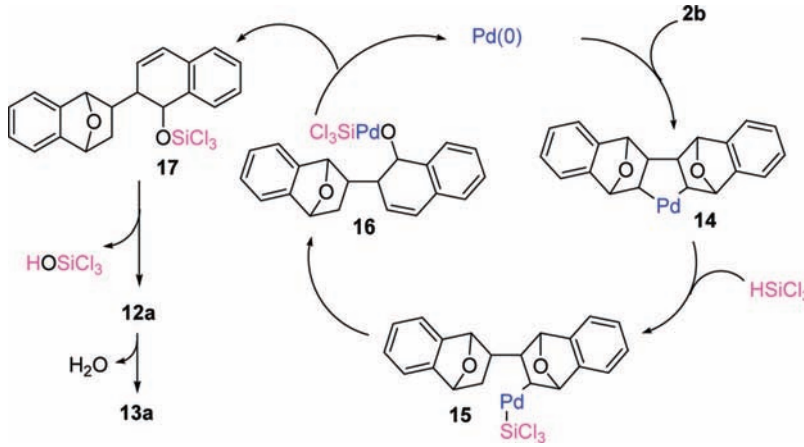


carbon–carbon bond is a powerful process for the synthesis of various alkyl and vinyl silanes. The reaction of 7-oxabenzonorbornadiene **2b** with trichlorosilane in toluene in the presence of $Pd(dba)_2$ at ambient temperature led rapidly (in ca. 1 min) to the formation of compound **12a** and 2,2′-binaphthyl (**13a**) in a 99:1 ratio in 86% combined yield (Scheme 5).[15a] No trace of the anticipated silyl addition product was observed. Compound **12a** was converted to **13a** if zinc powder or silica gel was added to the solution. Similarly, various 1,4-epoxy-1,4-dihydroarenes were converted to the corresponding biaryls **13** in good to excellent yields. Many of these biaryl products exhibit strong fluorescence. One of the products, bistriphenylene (BTP) **13c**, has been used as a powerful blue light emitter in organic light-emitting devices.[15b]

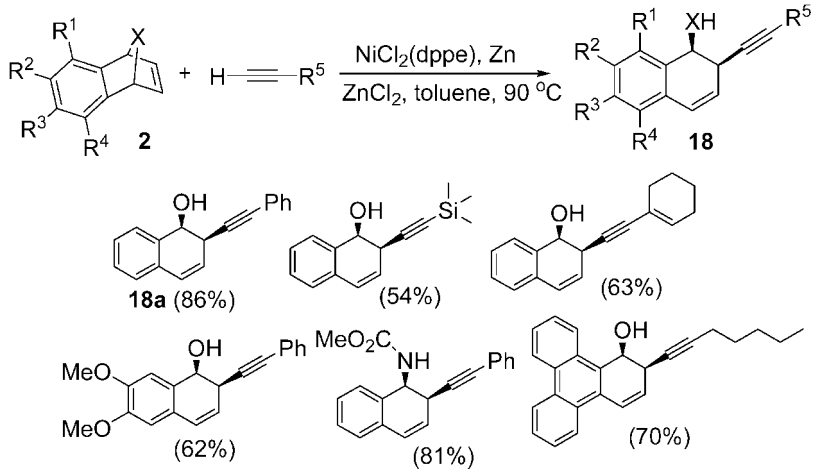
The process appears to occur via a novel palladium-catalyzed hydrosilylative dimerization of 1,4-epoxy-1,4-dihydroarenes and subsequent elimination of a $HOSiCl_3$ and H_2O molecule. A plausible pathway for the reaction involves the coordination of two molecules of **2b** to a Pd(0) species to give a palladacycle **14** (Scheme 6). Reaction of this five-membered palladacycle with $HSiCl_3$ via σ-bond metathesis and subsequent rearrangement gives product **13a**.

Terminal acetylenes can be added to bicyclic alkenes by using a nickel(II) complex and zinc as the catalyst (Scheme 7). Thus, treatment of 7-oxabenzonorbornadiene (**2b**) with phenylacetylene in the presence of $Ni(dppe)Cl_2$ and zinc in toluene at 90 °C gave **18a** in 54% yield along with a substantial amount of unidentified byproducts.[16] Addition of a catalytic amount of $ZnCl_2$ (0.20 mL of a 0.10 M solution) greatly increased the yield of product **18a** to 86%. A wide range of aliphatic and aromatic terminal acetylenes also participate in this highly stereoselective ring opening addition reaction. The mechanism (Scheme 8) likely involves a nickel(II)-catalyzed reaction with the initial steps involving the formation of zinc acetylide, which undergoes transmetalation with nickel(II) species to give nickel(II) acetylide **19**. The zinc metal used in the reaction serves

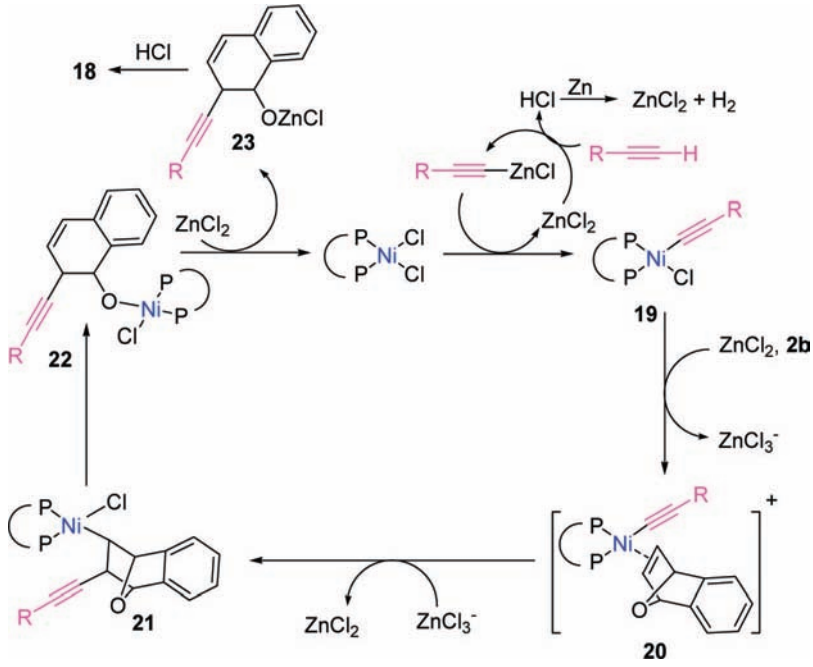
Scheme 6



Scheme 7

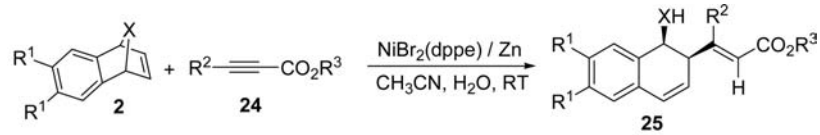


Scheme 8

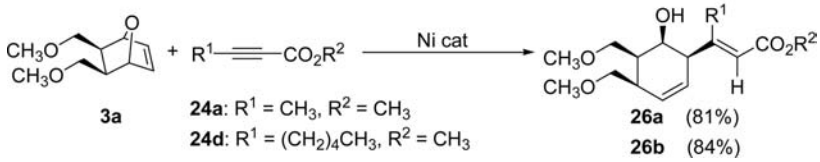


as an acid scavenger and assists in the formation of zinc acetylide. Zinc chloride also plays a role in the formation of cationic nickel complex **20** by abstracting a chloride ion. Zinc reagents acting as a Lewis acid to abstract a halide ion forming a cationic palladium complex was also proposed by Lautens et al.[17]

Scheme 9



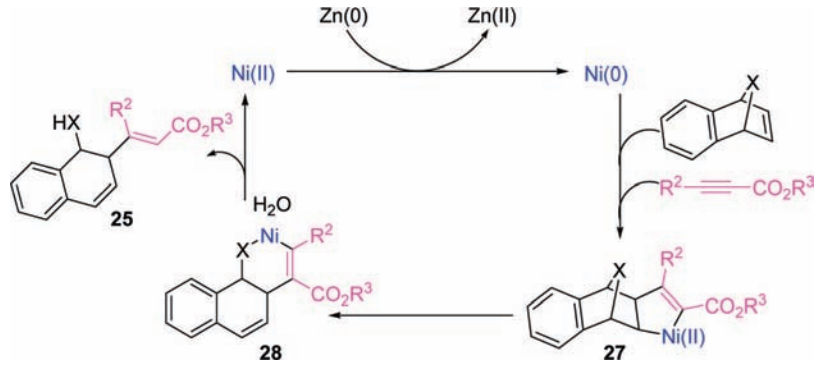
25a: R^1= H, R^2 = CH_3, R^3 = CH_3, X = O (91%)
25b: R^1= H, R^2 = *n*-Bu, R^3 = CH_3, X = O (86%)
25c: R^1= H, R^2 = TMS, R^3 = CH_2CH_3, X = O (76%)
25d: R^1= H, R^2 = H, R^3 = CH_2CH_3, X = O (59%)
25e: R^1= OCH_3, R^2 = CH_3, R^3 = CH_3, X = O (85%)
25f: R^1= OCH_3, R^2 = *n*-pentyl, R^3 = CH_3, X = O (89%)
25g: R^1= H, R^2 = CH_3, R^3 = CH_3, X = NCO_2CH_3 (78%)
25h: R^1= H, R^2 = *n*-Bu, R^3 = CH_3, X = NCO_2CH_3 (74%)



24a: R^1 = CH_3, R^2 = CH_3
24d: R^1 = $(CH_2)_4CH_3$, R^2 = CH_3

26a (81%)
26b (84%)

Scheme 10



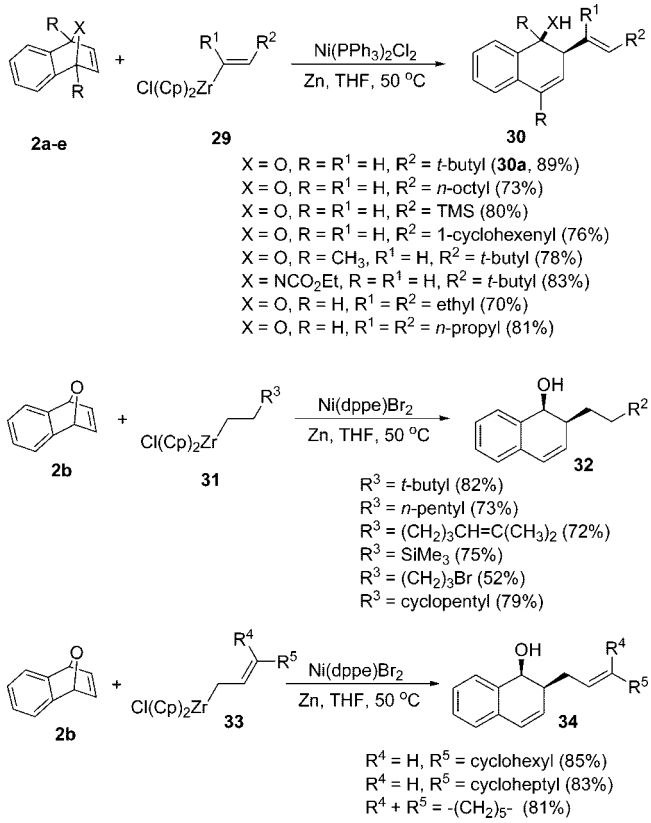
Internal alkynes also react with bicyclic alkenes catalyzed by nickel complexes, but in a different manner (vide infra). After various optimizing experiments, we found that propiolates underwent reductive ring opening coupling with oxa- and azabicyclic alkenes in the presence of a bidentate nickel phosphine complex to give products **25** with excellent regio- and stereoselectivity (Scheme 9).[18] Thus, the reaction of **2b** with methyl-2-butynoate in the presence of Ni(dppe)Br_2 and zinc powder in acetonitrile at room temperature gave **25a** in 60% yield. Addition of water greatly increases the yield to 91% (Scheme 9). Under similar reaction conditions, 7-oxabenzonorbornadiene also undergoes reductive coupling with various propiolates ($R^2C{\equiv}CCO_2R^3$) to give the corresponding *cis*-1,2-dihydronaphthalene derivatives **25b–f** in good to excellent yields. 7-Azabenzonorbornadiene also couples with propiolates cleanly to give **25g,h** in fair to good yields. In all these reactions, the products exhibit *trans* geometry on the alkenyl groups.

The catalytic reaction is successfully extended to substituted 7-oxanorbornenes. Thus, **3a** reacted with **24a** efficiently to give 3-cyclohexenol derivative **26a** with all substituents *cis* to each other in 81% yield (Scheme 9).

On the basis of the results described above and known nickel chemistry, the key pathways are proposed as shown in Scheme 10. The catalysis is initiated by the reduction of Ni(II) to Ni(0) by zinc powder. Exo coordination of 7-oxabenzonorbornadiene and propiolate to the Ni(0) center followed by regioselective oxidative coupling of the bicyclic alkene and alkyne leads to the formation of a nickel acyclopentene intermediate **27**. Subsequent β-heteroatom elimination and protonation afford the final product **25** and Ni(II) species. The latter is then reduced by Zn for regeneration of the Ni(0) species. This mechanism accurately accounts for the *cis* stereochemistry of the hydroxy and alkenyl groups and the *trans* geometry on the alkenyl moiety. Support for the protonation of **28** comes from the requirement of water in the reaction. In addition, an isotope labeling experiment using D_2O (99.5%) to replace H_2O in the synthesis of compound **25a** from **2b** and **24a** shows, by ^{1}H NMR analysis, that **25a** is labeled at the olefinic proton with a deuterium isotope abundance of 75%.

The addition of zirconium reagents to bicyclic alkenes is also successfully catalyzed by nickel complexes. Thus, the reaction of 7-oxabenzonorbornadiene (**2b**) with alkenylzirconium reagent **29a** in the presence of $NiCl_2(PPh_3)_2$ and zinc powder (10.0 mol %) in THF led to the formation of stereoselective ring opening addition product **30a** in 89% isolated yield (Scheme 11).[19] $NiBr_2(PPh_3)_2$ and $NiI_2(PPh_3)_2$ gave **30a** in only 42 and 15% yields, respectively. The most active nickel complex for this reaction

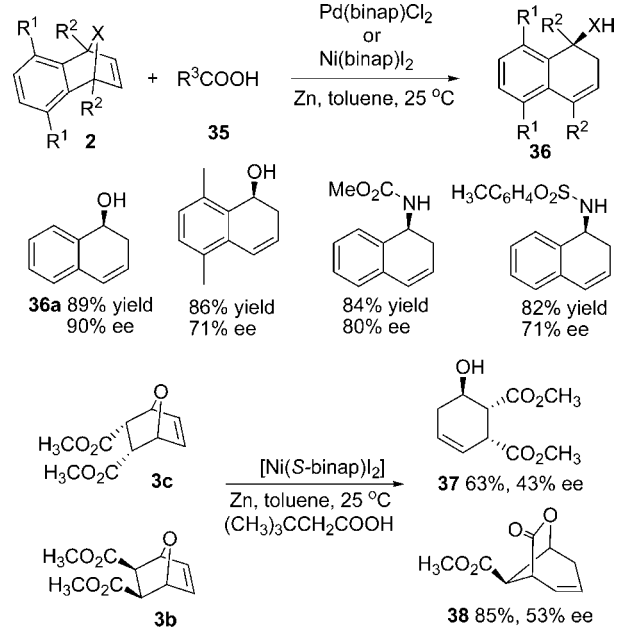
Scheme 11



appears to be $NiCl_2(PPh_3)_2$. Thus, the halide on nickel complex $NiX_2(PPh_3)_2$ has a profound effect on the yield of **30a**.[20] The reaction provides a convenient and general route to *cis*-2-alkenyl-1,2-dihydronaphthalene derivatives **30** in good to excellent yields and in high stereoselectivity from easily accessible starting materials. Internal alkenyl zirconium reagents also produce the corresponding ring opening products in good yields.

It is known that metal-catalyzed C_{sp^3}-$_{sp^3}$ bond formation reactions impose considerable synthetic limitations such as (a) slow oxidative addition, (b) transmetalation of the alkyl reagents to a metal center, and (c) rapid β-hydride elimination of the resulting alkylmetal complex. With the success of using alkenyl zirconium, we tested the addition of alkyl zirconium to bicyclic alkenes.[21] To our surprise, the use of $NiCl_2(PPh_3)_2$ as a catalyst under the standard conditions for alkenyl addition did not afford any desired product, but when the catalyst system was changed to bidentate phosphine complexes such as $NiBr_2$(dppe), the addition of alkylzirconium reagents to bicyclic alkenes proceeds effectively to give highly regio- and stereoselective *cis*-2-alkyl-1,2-dihydronaphthalene derivatives **32** (Scheme 11). The requirement of bidentate phosphine likely is associated with the inhibition of β-hydride elimination of the resulting alkylnickel complex, although the exact reason is not yet clear. A range of alkylzirconium reagents underwent ring opening reactions with **2b** to afford the corresponding ring opening products with high yields. This reaction is applicable to various longer and bulkier alkylzirconium reagents. In addition, this ring

Scheme 12

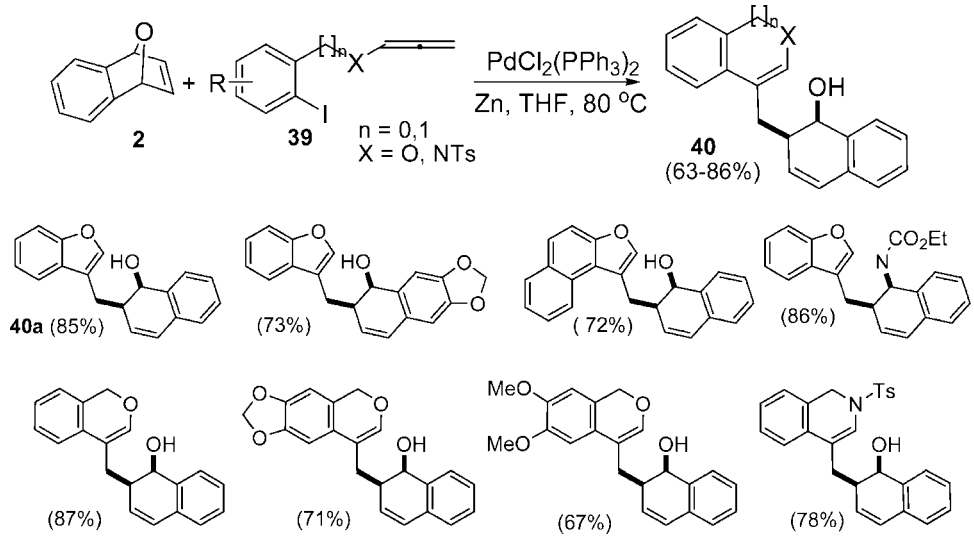


opening reaction is successfully extended into various allylzirconium reagents.

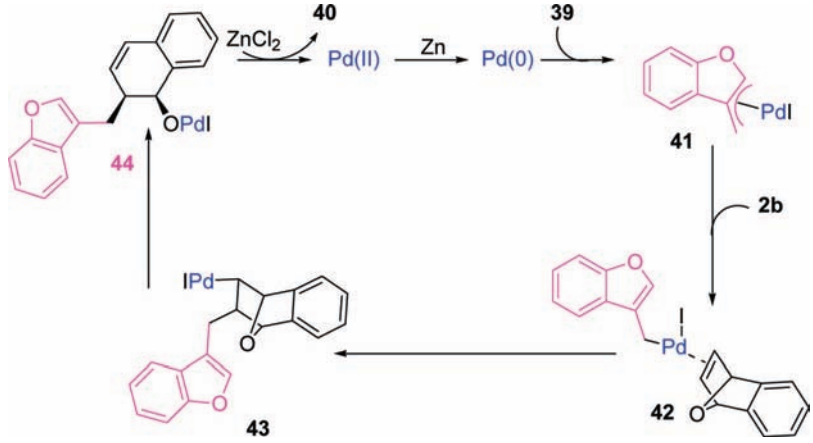
7-Oxabenzonorbornadiene (**2b**) undergoes reductive ring opening readily in the presence of a carboxylic acid, zinc metal, and a nickel or palladium phosphine complex (Scheme 12). For example, treatment of **2b**, acetic acid, and zinc using Ni(dppe)I_2 as a catalyst in THF at 20 °C afforded 1,2-dihydronaphth-1-ol (**36a**) in 94% yield.[22] With this result in hand, we tested the asymmetric version of this catalytic reaction by employing bidentate chiral ligands for the nickel and palladium catalysts. Thus, the reaction of **2b** with acetic acid in the presence of zinc and 5 mol % Pd(*R*-binap)Cl_2 as the catalyst in toluene at room temperature afforded (*S*)-1,2-dihydronaphth-1-ol in 90% yield with an enantiomeric excess (ee) of 77%. When the acid was changed from acetic acid to valproic acid (**35a**) [$(CH_3CH_2CH_2)_2CHCO_2H$], **36a** was obtained in 87% yield and 83% ee. The best result was obtained when valproic acid was stirred with the Pd catalyst and Zn for 1 h followed by addition of **2b**; the catalytic reaction gave **36a** in 89% yield with an ee of 90%. On the other hand, the reaction of **2b** with *tert*-butylacetic acid (**35b**) in the presence of 5 mol % Ni(*S*-binap)I_2 and zinc in acetonitrile at 25 °C for 2 h afforded (*R*)-1,2-dihydronaphth-1-ol in 89% yield and 77% ee. This nickel- and palladium-catalyzed asymmetric reductive ring opening offers a convenient and mild method for constructing enantiomerically enriched 1,2-dihydronaphth-1-ol in one pot from easily accessible starting material. Enantiopure 1,2-dihydronaphth-1-ol is an important precursor for the synthesis of sertraline, an antidepressant agent.[23]

The reductive ring opening strategy can be further applied to nonaromatic bicyclic systems. Reaction of bicyclic alkene **3c** with **35b** in the presence of Ni(*S*-binap)I_2 afforded a highly substituted cyclohexenol derivative **37** in 63% yield with 43% enantioselectivity.

Scheme 13



Scheme 14



Interestingly, for the reaction of **3b** (an exo isomer of **3c**) with **35b**, a bicyclo[3.2.1]lactone **38** was obtained instead in 85% yield and 53% ee (Scheme 12). Product **38** is likely formed via reductive ring opening of **3b**, followed by selective lactonization of the intermediate.

Very recently, we observed that oxa- or azabicyclic alkenes can be used as a versatile terminating agent in multistep reactions via a reductive ring opening addition reaction. When 2-iodophenoxyallene (**39a**) and oxabenzonorbornadiene (**2b**) were heated in the presence of $PdCl_2(PPh_3)_2$ and zinc powder in THF at 80 °C, product **40a** involving ring closure of **39a** and ring opening of **2b** was obtained in 85% isolated yield (Scheme 13).[24] Under these reaction conditions, 2-iodophenoxy-, 2-iodobenzyloxy-, and 2-iodobenzylaminoallenes successfully undergo ring closure followed by ring opening with various substituted bicyclic alkenes to give highly regio- and stereoselective products **40** with multiple stereocenters in high yields.

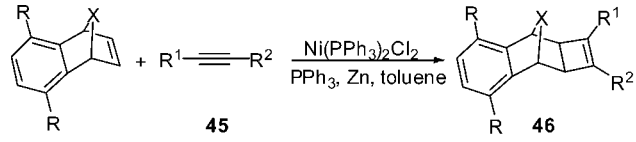
A possible mechanism for this catalytic reaction involves the reduction of $PdCl_2(PPh_3)_2$ to a Pd(0) by zinc metal and oxidative addition of 2-iodophenoxyallene **39** to Pd(0) followed by an intramolecular insertion of the allenyl group into the palladium–carbon bond to afford π-allyl palladium complex **41** (Scheme 14). Then, exo coordination and insertion of the carbon–carbon double bond of **2b** result in the formation of intermediate **43**. Subsequent β-oxy elimination and transmetalation with zinc halide lead to the final product **40** after hydrolysis. Pd(II) halide is then reduced by zinc metal powder to regenerate the Pd(0) catalyst.

Cycloaddition Reactions of Bicyclic Alkenes

The [2+2] cycloaddition of alkenes and alkynes, a powerful method for constructing four-membered rings, is thermally forbidden but can be achieved via photochemical reactions, by thermal reactions via biradical intermediates, with the assistance of Lewis acids or transition metal catalysts. We found that oxa- and azabenzonorbornadiene **2** underwent [2+2] cycloaddition with alkynes **45** in the presence of $NiCl_2(PPh_3)_2$, PPh_3, and zinc powder in toluene at 90 °C to give exo-cyclobutene derivatives **46** in high yields (Scheme 15).[25]

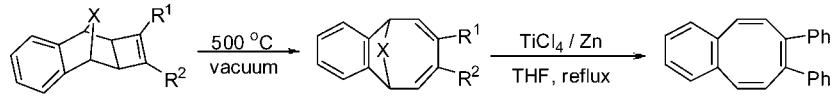
These cyclobutene derivatives undergo novel ring expansion, converting the fused four- or six-membered rings into an eight-membered cyclooctadiene moiety in high yields. For example, flash vacuum pyrolysis of **46a**

Scheme 15



45 **46**

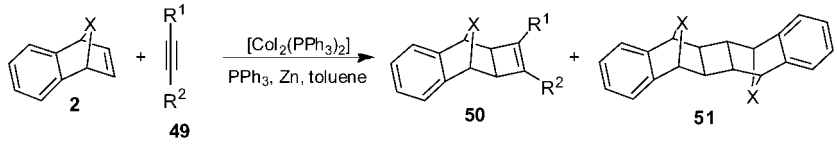
2b X = O, R = H
2c X = O, R = OCH_3
2a X = NCO_2Me, R = H



48a (89%)

46a X= O, $R^1 = R^2$ = Ph **47a** 85 %
46b X = O, R^1 = Ph, $R^2 = CO_2Et$ **47b** 70 %
46c X= O, $R^1 = R^2$ = Ph **47c** 80 %
40d X = NCO_2Me, $R^1 = R^2$ = Ph **41d** 96 %

Scheme 16



2 **49** **50** **51**

X= O, $R^1 = R^2 = CH_2CH_3$ **50a** 40 %
X = O, $R^1 = CH_3$, $R^2 = (CH_2)_2CH_3$ **50b** 35 %
X= O, $R^1 = CH_3$, $R^2 = CH_2CH_3$ **50c** 41%
X = NCO_2Me, $R^1 = R^2 = CH_2CH_3$ **50d** 55 %
X = NCO_2Me, $R^1 = CH_3$, $R^2 = (CH_2)_2CH_3$ **50e** 63 %

at 500 °C readily affords diene **47a** in 85% yield with 99% selectivity. Subsequent deoxygenation of **47a** with $TiCl_4$ and Zn affords cyclooctatetraene derivative **48a** in 89% yield.

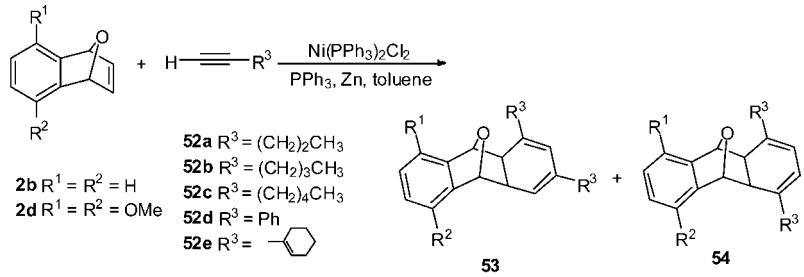
It is noteworthy that under nickel-catalyzed conditions, dialkylacetylenes did not undergo [2+2] cycloaddition with bicyclic alkenes. This led us to test the activity of the cobalt system, $CoI_2(PPh_3)_2$/Zn, for the [2+2] cycloaddition of oxa- and azabenzonorbornadiene **2**.[26] The Co system is effective with a variety of alkynes. In addition, it is also active for the [2+2] cycloaddition of dialkylacetylenes **49** with bicyclic alkenes **2** which gives the corresponding cyclobutenes, albeit in lower yields (Scheme 16). The poor reactivity of dialkyl acetylenes compared with those of other acetylenes allows oxabenzonorbornadiene **2** to undergo [2+2] self-dimerization readily. [27]

When 7-oxabenzonorbornadiene was treated with terminal aliphatic alkynes in the presence of $NiCl_2(PPh_3)_2$, PPh_3, and zinc powder in toluene at room temperature, [2+2+2] cocyclotrimerization adducts were obtained instead (Scheme 17). For example, the reaction of oxabenzonorbornadiene (**2b**) with 1-pentyne (**52a**) at 18 °C afforded a pair of regioisomers, **53a** and **54a**, in excellent combined yield,[28] whereas the reaction of terminal acetylenes with bulkier substituents such as phenyl acetylene (**52d**) and 1-ethynyl-1-cyclohexene (**52e**) afforded regioselectively only **53d** and **53e**, respectively, in high yields. Similarly, other substituted olefins also underwent smoothly the cocyclotrimerization with alkynes to afford the desired products.

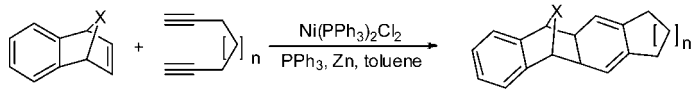
Interestingly, the reaction of diynes with oxanorbornadiene gave the [2+2+2] cocyclotrimerization products with multiple fused rings under similar reaction conditions in good yields (Scheme 17). Thus, 1,6-heptadiyne (**55a**) and 1,7-octadiyne (**55b**) reacted with **2b** and **2e** to afford novel pentacyclic adducts **56a–d** in 62–75% yields.

The nickel-catalyzed [2+2+2] cycloaddition not only provides an excellent method for constructing multiple fused rings but also elucidates two other synthetic applications. First, these products can be used as convenient precursors for isobenzofurans and isoindoles (Scheme 18). For example, heating **56c** and **56d** with **2b** led to the isolation of the Diels–Alder cycloaddition product of isoindole **58** in 70% yield. Treatment of **56a** with cyclohex-2-en-1-one in toluene at 60 °C afforded endo and exo isomers of the Diels–Alder cycloadducts **59** and **60** (ca. 1:1) in 77% combined yield. Second, this [2+2+2] cycloaddition can be employed to synthesize aromatic compounds (Scheme 18) in which compound **2b** serves as "masked acetylene". The cycloaddition of **2b** and methyl but-2-ynoate in the presence of the nickel catalyst demonstrates both applications. The reaction produced aromatic compound **61** regioselectively and the Diels–Alder cycloadducts **62** and **63** from isobenzofuran (**57**) generated in situ and **2b**. Furthermore, the nickel-catalyzed [2+2+2] methodology was applied to the reaction of fullerene C_{60} with diynes to yields fullerene derivatives consisting of a cyclohexadiene ring.[29] Similarly, this methodology was further applied to the reaction of acrylates,[30] allenes,[31] and conjugate diynes[32] with alkynes.

Scheme 17



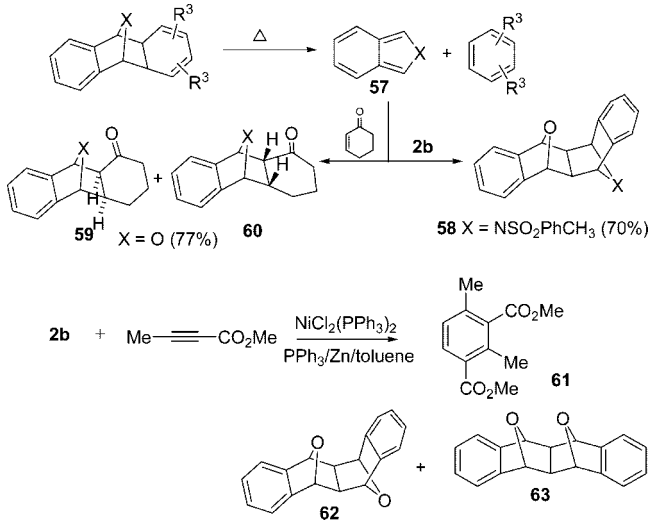
Entry	Substrate	Temp/ °C	Alkyne	Product (yield %)
1)	**2b**	18	**52a**	**53a** (22) + **54a** (69)
2)	**2b**	18	**52b**	**53b** (29) + **54b** (62)
3)	**2b**	18	**52c**	**53c** (7) + **54c** (61)
4)	**2b**	-5	**52d**	**53d** (95)
5)	**2b**	18	**52e**	**53e** (95)
6)	**2d**	0	**52d**	**53f** (74)



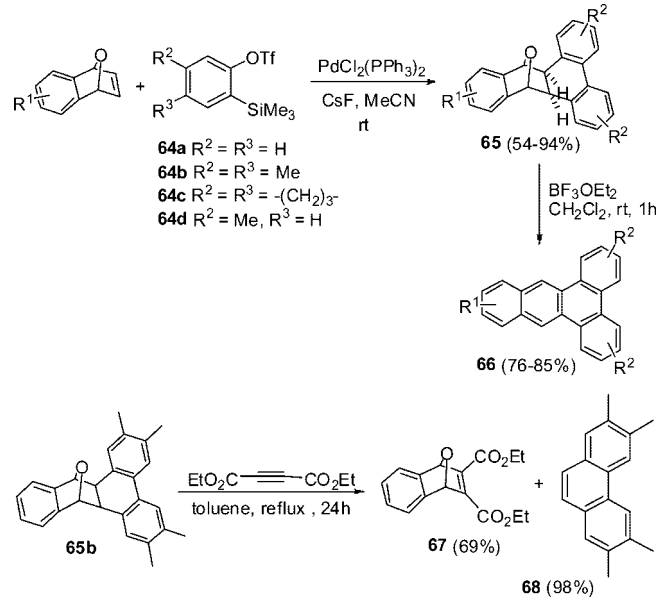
2b X = O **55a** n = 1
2e X = NSO_2Ph-*p*-CH_3 **55b** n = 2

56a X = O, n = 1 62 %
56b X = O, n = 2 70 %
56c X = NSO_2Ph-*p*-CH_3, n = 1 71 %
56d X = NSO_2Ph-*p*-CH_3, n = 2 75 %

Scheme 18



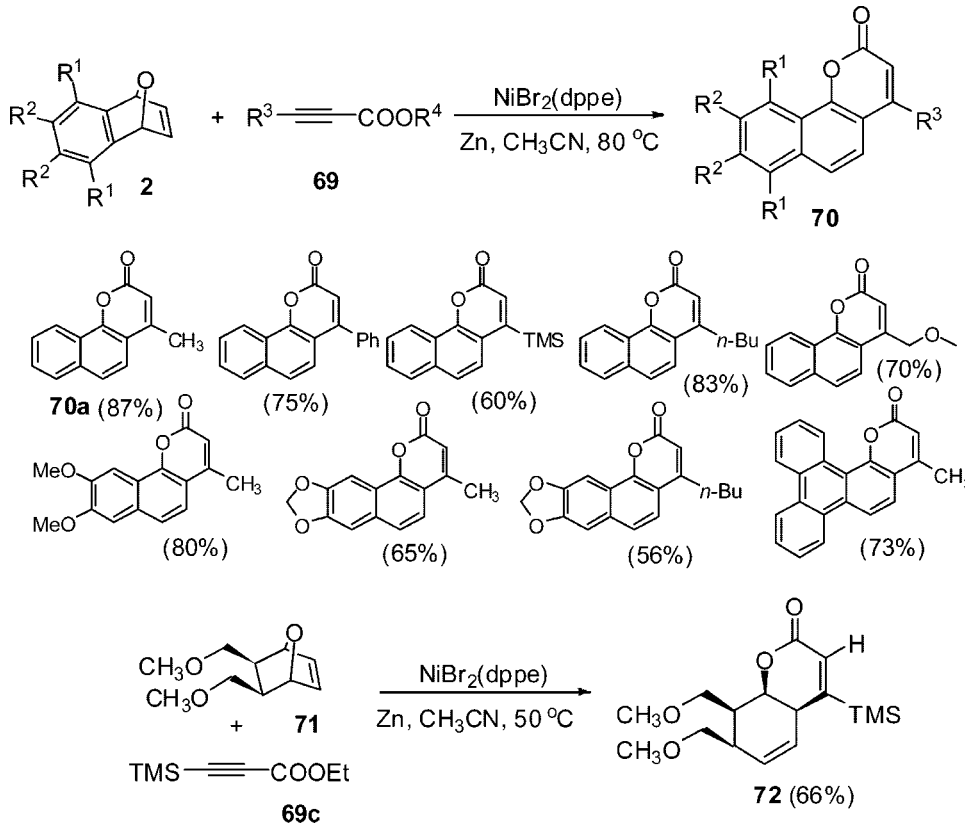
Scheme 19



Arynes can also be employed in the [2+2+2] cocyclotrimerization involving bicyclic alkene. Treatment of 7-oxabenzonorbornadiene (**2b**) with aryne precursor 2-(trimethylsilyl)phenyl triflate (**64a**) and CsF in the presence of $PdCl_2(PPh_3)_2$ in acetonitrile at ambient temperature yielded [2+2+2] cocyclotrimerization product **65a** in 94% yield (Scheme 19).[33] This palladium-catalyzed cocyclotrimerization was successfully extended to different bicyclic alkenes and arynes, affording annulated 9,10-dihydrophenanthrene derivatives **65** in good yields. Furthermore, these cycloadduct products undergo deoxyaromatization readily with the help of Lewis acid BF_3OEt_2 at room temperature, providing a simple yet efficient route to various substituted polycyclic aromatic hydrocarbons **66**.

When product **65b** was refluxed in toluene in the presence of diethyl acetylenedicarboxylate, cycloadduct **67** and the substituted phenanthrene **68** were obtained in high yields. This method provides a convenient route for new precursors of isobenzofurans and for the synthesis of phenanthrenes with no substituent at the 9- and 10-positions. It is noteworthy that all previously reported constructions of phenanthrene via aryne invariably have substituents at the 9- and 10-positions of the phenanthrene ring in addition to other substituents.

Scheme 20

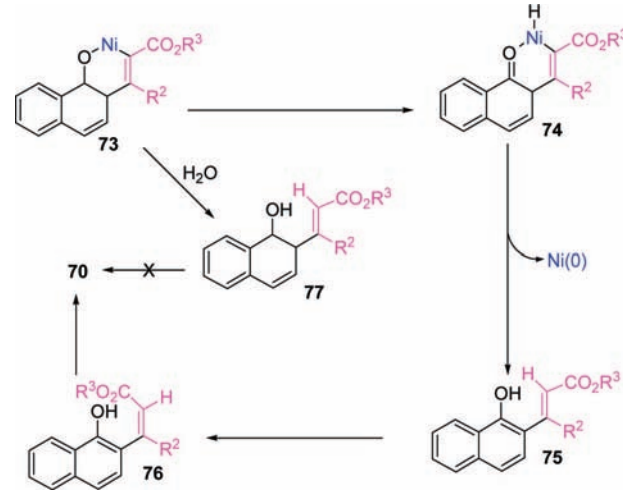


Cyclization Reactions Involving Bicyclic Alkenes

Oxabicyclic alkenes undergo cyclization with alkyl propiolates at 80 °C catalyzed by bidentate phosphine nickel complexes to give benzocoumarin derivatives in high yields. For example, treatment of 7-oxabenzonorbornadiene (**2b**) with methyl butyn-2-oate (**69a**) in the presence of $NiBr_2$(dppe) and zinc metal powder in acetonitrile at 80 °C gave a benzocoumarin product **70a** in 87% yield (Scheme 20).[34] Other bidentate phosphines, dppf, dppm, and dppp, are less effective, and monodentate phosphine either exhibited no activity or gave different products (see Schemes 15 and 18). The choice of solvent is also vital to the catalytic reaction. The best solvent is acetonitrile. DMF is also effective (44% yield). As shown in Scheme 20, a variety of substituted alkyl propiolates **69** ($R^1C{\equiv}CCO_2R^2$) can react with substituted 7-oxabenzonorbornadienes to give the corresponding benzocoumarin derivatives in good yields. The cyclization of substituted 7-oxanorbornene **71** with $TMSC{\equiv}CCO_2Et$ **69c** in CH_3CN at 50 °C also proceeded smoothly in completely regio- and stereoselective fashion to give tetrahydrocoumarin **72** in 66% yield.

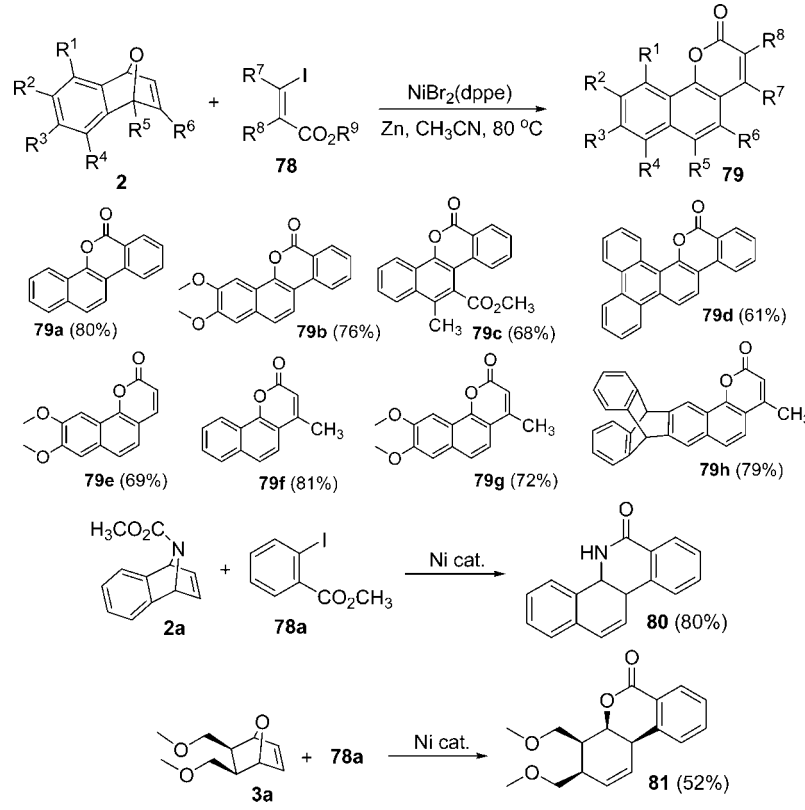
The mechanism for benzocoumarin formation is interesting in view of the extensive bond formation and breaking processes that are required. While the detailed pathways are not clear, the initial few steps and intermediate **73** are expected to be similar to those in Scheme 10.[35,36] A possible route for the conversion of **73** to the final product **70** is shown in Scheme 21. Rearrangement of **73** via β-hydride elimination to give **74**, enolization to give **75**, *cis–trans* isomerization, and lactonization afford **70**. Attempts to convert the ring opening reductive coupling product **77** to benzocoumarin **70** failed under the catalytic conditions.

Scheme 21

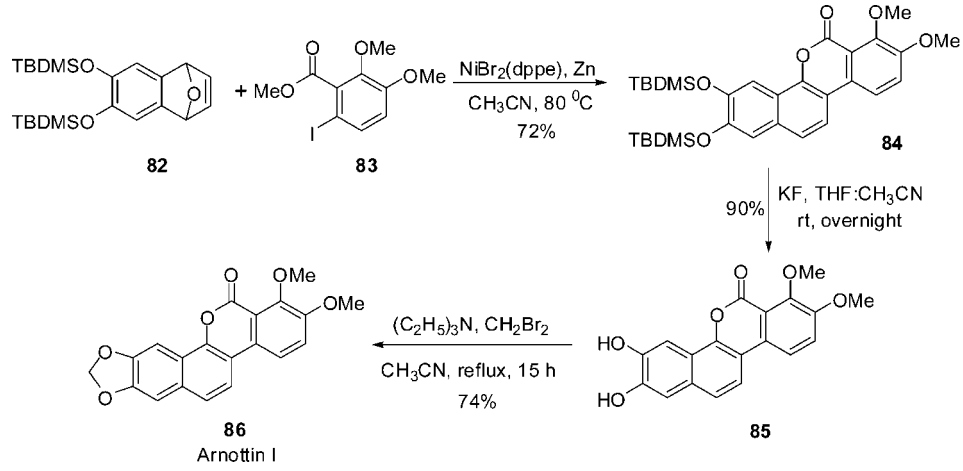


While this method offers a convenient route to the synthesis of 3-subtituted benzocourmarins, a complementary method was developed providing a pathway for more substituted benzocoumarins (Scheme 22). In the presence of Ni(dppe)Br_2 and Zn powder in acetonitrile at 80 °C, oxabicyclic alkenes undergo cyclization with *o*-iodobenzoate to give structurally complicated dibenzocoumarin derivatives (**79b–d**) in one pot in moderate to good yields.[37]

Scheme 22



Scheme 23

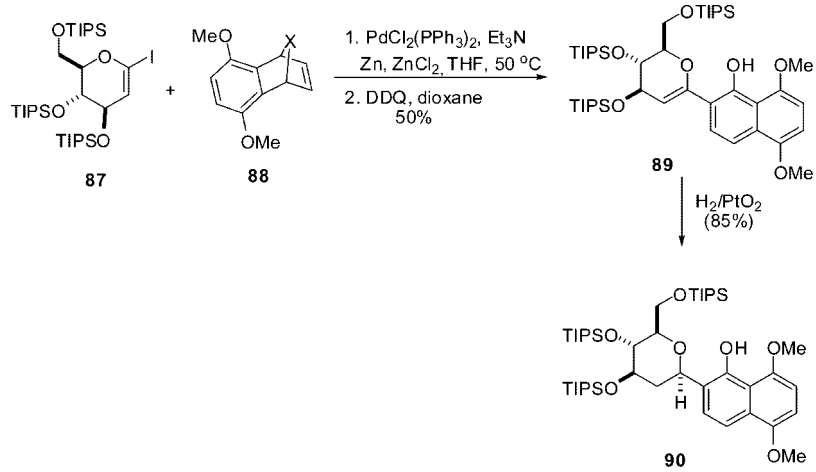


β-Iodo-(*Z*)-propenoates were also successfully employed in this nickel-catalyzed cyclization process to give the corresponding benzocoumarins (**79e–h**). Similar to oxabicyclic olefins, azabenzonorbornadiene **2a** reacted with **78a** cleanly, affording lactam **80** in 80% yield (Scheme 20). Unlike coumarin products **79**, **80** is not dehydrogenated, but the carbamate group was replaced with a hydrogen during the course of the reaction. The cyclization of substituted 7-oxanorbornene **3a** with **78a** also occurs readily, leading to the formation of tetrahydrocoumarin **81** in a completely stereoselective fashion.

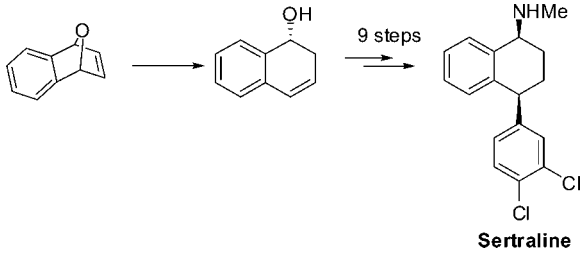
We have applied the nickel-catalyzed methodology for the total synthesis of arnottin I, first isolated from *Xanthoxylum arnottianum* Maxim.[38] Arnottin I is a coumarin-based natural product found in gilvocarcin-type antibiotics. TBDMS-protected oxabenzonorbornadiene **82** was synthesized in three steps starting from catechol in 44% yield (Scheme 23). Compound **82** was then reacted with *o*-iodobenzoate **83** to give the corresponding coumarin derivative **84**. The silyl groups were successfully removed by KF (10.0 equiv) in a mixture of THF and CH_3CN (1:1 by volume) to give dihydroxy derivative **85**. Ring closure was carried out using triethylamine and CH_2Br_2 in CH_3CN under reflux to furnish arnottin I **86** (Scheme 23).[39] On the whole, arnottin I **86** was obtained in 21% yield over six steps from catechol.

Applications of ring opening/coupling methodologies to the synthesis of biologically important molecules have been demonstrated by other groups as well. Recently,

Scheme 24



Scheme 25



Martin's group reported a general protocol for the synthesis of the *C*-aryl glycosides via a ring opening approach as outlined in Scheme 24.[40] The reaction of **87** with **88** proceeded readily under the palladium conditions to give a diastereomeric mixture (1:1) of *cis*-dihydronaphthol derivatives. The oxidation of the mixture with recrystallized DDQ gave naphthol **89**. Hydrogenation of **89** then delivered a group II *C*-aryl glycoside **90** as a single diastereomer. Similarly, this methodology was applied for the synthesis of group III *C*-aryl glycoside model structures. More recently, the same group has come up with modified conditions for the palladium-catalyzed coupling and oxidations to afford more better yields of *C*-aryl glycosides.

Earlier, Lautens' group developed and applied the enantioselective reductive ring opening of oxabenzonorbornadiene to the total synthesis of the clinically important antidepressant agent sertraline.[23] The enantiopure dihydronaphthol product from ring opening was converted in nine steps to sertraline in 33% overall yield (Scheme 25).

Conclusion

We have demonstrated that nickel- and palladium-catalyzed reactions of oxa- and azabicyclic olefins with alkynes, benzynes, propiolates, zirconium reagents, and *o*-halobenzene derivatives occur with excellent selectivity and yields. These reactions involve cycloaddition, cyclization, and coupling and provide synthetically and biologically useful compounds in one pot. The methodologies have found use in the total synthesis of biologically interesting molecules, such as arnottin I, and also in the synthesis of emitters for organic light-emitting devices. Our current studies are focused on expanding the scope of these reactions, the application of the methodologies to the synthesis of natural products, and understanding the mechanisms of these catalytic reactions in detail.

The work reported in this Account would not have been possible without the efforts of the co-workers whose names appear in the references. In particular, we acknowledge the contributions of Jiun-Pey Duan, Daw Jen Huang, Lih-Ping Li, and Dinesh Rayabarapu for initiating bicyclic olefin chemistry. This research was generously supported by the National Science Council, Republic of China. We are also thankful to the reviewers for suggesting important changes in the manuscript.

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